AMENDMENT

Listing of the Claims:

The following listing of claims replaces all previous listings or version thereof:

1. (Original) A method of treating pathologic cardiac hypertrophy or heart failure comprising:

   (a) identifying a patient having cardiac hypertrophy or heart failure; and
   (b) administering to said patient an inhibitor of Protein Kinase D (PKD)

2. (Original) The method of claim 1, wherein said inhibitor of PKD is selected from the group consisting of resveratrol, indolocarbazoles, Godecke 6976 (Go6976), staurosporine, K252a, Substance P (SP) analogues including [d-Arg(1),d-Trp(5,7,9), Leu(11)]SP, PKC inhibitor 109203X (GF-1), PKC inhibitor Ro 31-8220, GO 7874, Genistein, the specific Src inhibitors PP-1 and PP-2, chelerythrine, rottlerin, a PKD RNAi molecule, a PKD antisense molecule, a PKD ribozyme molecule or a PKD-binding single-chain antibody, or expression construct that encodes a PKD-binding single-chain antibody.

3. (Original) The method of claim 1, wherein administering the inhibitor of PKD is performed intravenously or by direct injection into cardiac tissue.

4. (Original) The method of claim 1, wherein administering comprises oral, transdermal, sustained release, controlled release, delayed release, suppository, or sublingual administration.

5. (Original) The method of claim 1, further comprising administering to said patient a second cardiac hypertrophic therapy.

6. (Original) The method of claim 5, wherein said second therapy is selected from the group consisting of a beta blocker, an ionotrope, a diuretic, ACE-I, AII antagonist, BNP, a Ca^{++}-blocker, or an HDAC inhibitor.

7. (Original) The method of claim 5, wherein said second therapy is administered at the same time as said inhibitor of PKD.

8. (Original) The method of claim 5, wherein said second therapy is administered either before or after said inhibitor of PKD.

9. (Original) The method of claim 1, wherein treating comprises improving one or more symptoms of pathologic cardiac hypertrophy.

10. (Original) The method of claim 1, wherein treating comprises improving one or more symptoms of heart failure.

11. (Original) The method of claim 9, wherein said one or more improved symptoms comprises increased exercise capacity, increased cardiac ejection volume, decreased left ventricular end diastolic pressure, decreased pulmonary capillary wedge pressure, increased cardiac output, or cardiac index, lowered pulmonary artery pressures, decreased left ventricular end systolic and diastolic dimensions, decreased left and right ventricular wall stress, decreased wall tension, increased quality of life, and decreased disease related morbidity or mortality.

12. (Original) A method of preventing pathologic hypertrophy or heart failure comprising:

(a) identifying a patient at risk of developing pathologic cardiac hypertrophy or heart failure; and
(b) administering to said patient an inhibitor of PKD.

13. (Original) The method of claim 12, wherein said inhibitor of PKD is selected from the group consisting of resveratrol, indolocarbazoles, Godecke 6976 (Go6976), staurosporine, K252a, Substance P (SP) analogues including [d-Arg(1),d-Trp(5,7,9), Leu(11)]SP, PKC inhibitor 109203X (GF-1), PKC inhibitor Ro 31-8220, PKC inhibitor GO 7874, Genistein, the specific Src inhibitors PP-1 and PP-2, chelerythrine, rottlerin, a PKD RNAi molecule, a PKD antisense molecule, a PKD ribozyme molecule or a PKD-binding single-chain antibody, or expression construct that encodes a PKD-binding single-chain antibody.

14. (Original) The method of claim 12, wherein administering the inhibitor of PKD is performed intravenously or by direct injection into cardiac tissue.

15. (Original) The method of claim 12, wherein administering comprises oral, transdermal, sustained release, controlled release, delayed release, suppository, or sublingual administration.

16. (Original) The method of claim 12, wherein the patient at risk may exhibit one or more of a list of risk factors comprising long standing uncontrolled hypertension, uncorrected valvular disease, chronic angina, recent myocardial infarction, congenital predisposition to heart disease or pathological hypertrophy.

17. (Original) The method of claim 12, wherein the patient at risk may be diagnosed as having a genetic predisposition to cardiac hypertrophy.

18. (Original) The method of claim 12, wherein the patient at risk may have a familial history of cardiac hypertrophy.

19. (Original) A method of assessing an inhibitor of PKD for efficacy in treating cardiac hypertrophy or heart failure comprising:

(a) providing an inhibitor of PKD;
(b) treating a cell with said inhibitor of PKD; and
(c) measuring the expression of one or more cardiac hypertrophy parameters,

wherein a change in said one or more cardiac hypertrophy parameters, as compared to one or more cardiac hypertrophy parameters in a cell not treated with said inhibitor of PKD, identifies said inhibitor of PKD as an inhibitor of cardiac hypertrophy or heart failure.

20. (Original) The method of claim 19, wherein said cell is a myocyte.

21. (Original) The method of claim 19, wherein said cell is an isolated myocyte.

22. (Original) The method of claim 21, wherein said myocyte is a cardiomyocyte

23. (Original) The method of claim 20, wherein said myocyte is comprised in isolated intact tissue.

24. (Original) The method of claim 20, wherein said myocyte is a neonatal rat ventricular myocyte.

25. (Original) The method of claim 19, wherein said cell is an H9C2 cell.

26. (Original) The method of claim 22, wherein said cardiomyocyte is located *in vivo* in a functioning intact heart muscle.

27. (Original) The method of claim 26, wherein said functioning intact heart muscle is subjected to a stimulus that triggers a hypertrophic response in one or more cardiac hypertrophy parameters.

28. (Original) The method of claim 27, wherein said stimulus is aortic banding, rapid cardiac pacing, induced myocardial infarction, or transgene exression.

29. (Original) The method of claim 27, wherein said stimulus is a chemical or pharmaceutical agent.

30. (Original) The method of claim 29, wherein said chemical or pharmaceutical agent comprises angiotensin II, isoproterenol, phenylepherine, endothelin-I, vasoconstrictors, antidiuretics.

31. (Original) The method of claim 27, wherein said one or more cardiac hypertrophy parameters comprises right ventricular ejection fraction, left ventricular ejection fraction, ventricular wall thickness, heart weight/body weight ratio, right or left ventricular weight/body weight ratio, or cardiac weight normalization measurement.

32. (Original) The method of claim 20, wherein said myocyte is subjected to a stimulus that triggers a hypertrophic response in said one or more cardiac hypertrophy parameters.

33. (Original) The method of claim 32, wherein said stimulus is expression of a transgene.

34. (Original) The method of claim 32, wherein said stimulus is treatment with a drug.

35. (Original) The method of claim 19, wherein said one or more cardiac hypertrophy parameters comprises the expression level of one or more target genes in said myocyte, wherein expression level of said one or more target genes is indicative of cardiac hypertrophy.

36. (Original) The method of claim 35, wherein said one or more target genes is selected from the group consisting of ANF, α-MyHC, β-MyHC, α-skeletal actin, SERCA, cytochrome oxidase subunit VIII, mouse T-complex protein, insulin growth factor binding protein, Tau-microtubule-associated protein, ubiquitin carboxyl-terminal hydrolase, Thy-1 cell-surface glycoprotein, or MyHC class I antigen.

37. (Original) The method of claim 35, wherein the expression level is measured using a reporter protein coding region operably linked to a target gene promoter.

38. (Original) The method of claim 37, wherein said reporter protein is luciferase, β-gal, or green fluorescent protein.

39. (Original) The method of claim 35, wherein the expression level is measured using hybridization of a nucleic acid probe to a target mRNA or amplified nucleic acid product.

40. (Original) The method of claim 19, wherein said one or more cardiac hypertrophy parameters comprises one or more aspects of cellular morphology.

41. (Original) The method of claim 40, wherein said one or more aspects of cellular morphology comprises sarcomere assembly, cell size, or cell contractility.

42. (Original) The method of claim 19, wherein said one or more cardiac hypertrophy parameters comprises total protein synthesis.

43. (Original) The method of claim 19, further comprising measuring cell toxicity.

44. (Original) The method of claim 19, wherein said cell expresses a mutant class II HDAC protein lacking one or more phosphorylation sites.

45. (Original) The method of claim 19, wherein said measuring comprises measuring the activity or expression of a gene selected from the group consisting of an atrial natriuretic factor gene, a β-myosin heavy chain gene, a cardiac actin gene and an α-skeletal actin gene.

46. (Original) The method of claim 19, wherein said measuring comprises measuring the phosphorlyation of class-II HDAC's.

47. (Original) The method of claim 19, wherein said measuring comprises measuring the nuclear export of class-II HDAC's.

48. (Original) The method of claim 19, wherein said measuring comprises measuring the association of class-II HDAC's and Mef-2.

49. (Original) The method of claim 48, wherein the measuring further comprises measuring for an enhancement of class-II HDAC association with Mef-2.

50. (Original) The method of claim 49, wherein said enhancement is measured by an increase in Mef-2 dependent transcription.

51. (Original) The method of claim 19, wherein said treating is performed *in vitro*.

52. (Original) The method of claim 19, wherein said treating is performed *in vivo*.

53. (Original) The method of claim 19, wherein said cell is part of a transgenic, non-human mammal.

54. (Original) A method of identifying an inhibitor of cardiac hypertrophy or heart failure comprising:

(a) providing a PKD;
(b) contacting the PKD with a candidate inhibitor substance; and
(c) measuring the kinase activity of said PKD,

wherein a decrease in the kinase activity of the PKD identifies said candidate inhibitor substance as an inhibitor of cardiac hypertrophy or heart failure.

55. (Original) The method of claim 54, where said PKD is purified away from whole cells.

56. (Original) The method of claim 55, wherein said cells are heart cells.

57. (Original) The method of claim 54, wherein said PKD is located in an intact cell.

58. (Original) The method of claim 57, wherein said intact cell is a myocyte.

59. (Original) The method of claim 58, wherein said myocyte is a cardiomyocyte.

60. (Original) The method of claim 54, wherein a decrease in kinase activity is measured as a decrease in phosphorylation of HDAC.

61. (Original) The method of claim 60, wherein HDAC is a class-II HDAC.

62. (Original) The method of claim 54, wherein the candidate inhibitor substance is an interfering RNA.

63. (Original) The method of claim 54, wherein the candidate inhibitor substance is an antibody preparation.

64. (Original) The method of claim 63, wherein the antibody preparation comprises single chain antibodies.

65. (Original) The method of claim 54, wherein the candidate inhibitor substance is an antisense construct.

66. (Original) The method of claim 54, wherein said inhibitor is an enzyme, chemical, pharmaceutical, or small compound.

67. (Original) The method of claim 54, wherein said inhibitor of PKD is selected from the group consisting of resveratrol, indolocarbazoles, Godecke 6976 (Go6976), staurosporine, K252a, Substance P (SP) analogues including [d-Arg(1),d-Trp(5,7,9), Leu(11)]SP, PKC inhibitor 109203X (GF-1), PKC inhibitor Ro 31-8220, GO 7874, Genistein, the specific Src inhibitors PP-1 and PP-2, chelerythrine, rottlerin.

68. (Original) The method of claim 54, wherein said inhibitor blocks binding of PKD to class II HDAC's.

69. (Original) The method of claim 68, wherein the method of the blockage of binding is measured by co-immunoprecipitation.

70. (Original) The method of claim 54, wherein said inhibitor blocks PKD phosphorylation of class II HDAC's.

71. (Original) The method of claim 54, wherein said inhibitor enhances HDAC association with Mef-2 or other class II HDAC regulated transcription factors.

72. (Original) A transgenic, non-human mammal, the cells of which comprise a heterologous PKD gene under the control of a promoter active in eukaryotic cells.

73. (Original) The transgenic mammal of claim 72, wherein said mammal is a mouse.

74. (Original) The transgenic mammal of claim 72, wherein said heterologous PKD gene is human.

75. (Original) The transgenic mammal of claim 72, wherein said promoter is a tissue specific promoter.

76. (Original) The transgenic mammal of claim 75, wherein the tissue specific promoter is a muscle specific promoter.

77. (Original) The transgenic mammal of claim 75, wherein the tissue specific promoter is a heart muscle specific promoter.

78. (Original) The transgenic mammal of claim 75, wherein the muscle specific promoter is selected from the group consisting of myosin light chain-2 promoter, alpha actin promoter, troponin 1 promoter, Na^{+}/Ca^{2+} exchanger promoter, dystrophin promoter, creatine kinase promoter, alpha7 integrin promoter, brain natriuretic peptide promoter, myosoin heavy chain promoter, ANF promoter, and alpha B-crystallin/small heat shock protein promoter.

79. (Original) The transgenic mammal of claim 72, wherein said kinase is constitutively active.

80. (Original) The transgenic mammal of claim 72, wherein said kinase is a dominant negative.

81. (Original) A transgenic, non-human mammal, the cells of which comprise a PKD gene under the control of a heterologous promoter active in the cells of said non-human mammal.

82. (Original) The transgenic mammal of claim 81, wherein said mammal is a mouse.

83. (Original) The transgenic mammal of claim 81, wherein said PKD gene is human.

84. (Original) The transgenic mammal of claim 83, wherein said promoter is active in eukaryotic cells.

85. (Original) The transgenic mammal of claim 84, wherein said promoter is a tissue specific promoter.

86. (Original) The transgenic mammal of claim 85, wherein the tissue specific promoter is a muscle specific promoter.

87. (Original) The transgenic mammal of claim 85, wherein the tissue specific promoter is a heart muscle specific promoter.

88. (Original) A transgenic, non-human mammal, the cells of which lack one or both native PKD alleles.

89. (Original) The mammal of claim 88, wherein one or more genes have been knocked out by homologous recombination.

90-99. (Canceled)

100. (New) The method of Claim 1, wherein treating pathologic cardiac hypertrophy or heart failure further comprises increasing exercise tolerance, reducing hospitalizations, improving quality of life, decreasing morbidity, or decreasing mortality in a subject with heart failure or cardiac hypertrophy.